REMARKS

Status of the Claims and Claim Amendments

As of the recent office action dated December 27, 2007, claims 1, 8, 14-16, and 18-35 were pending in the application. Claims 14-16 and 18-22 were withdrawn from consideration, and claims 1, 8, and 23 - 35 were under prosecution. Applicant takes this opportunity to thank the Office for the withdrawal of the previous objection to claim 8 and rejection to claim 1 under 35 U.S.C. § 102(e).

In the instant office action, claims 1, 8, and 23 - 35 are rejected. Claims 8, 30 and 31 are objected to. By way of this response, claims 8, 23, 24, 30, and 31 are amended. Support for the amendments can be found throughout the specification and claims as originally filed (hereinafter the "Specification").

Upon entry of the amendment, claims 1, 8, and 23 – 35 will be pending and under prosecution, with claims 1 and 8 being the independent claims. Applicants submit that all pending claims are in condition for allowance.

The foregoing amendments do not constitute an admission regarding the patentability of the amended subject matter and should not be so construed. Applicant reserves the right to pursue the subject matter of the canceled claims in this or any other appropriate patent application.

I. Provisional Objections to Claims 23-26

Claims 30-32 were provisionally objected to. Specifically, the Office asserted that should claims 23-26 be found allowable, claims 30-32 will be objected to under 37 CFR § 1.75 as being a substantial duplicate thereof. Applicant submits that the amendment to claim 30 renders these objections moot. Thus, Applicant respectfully requests that the objections be withdrawn.

II. Objection to Claims 8, 30 and 31

Claims 8, 30, and 31 were objected to because the claims contain inadvertent grammatical errors. The word "one" has been inserted after "said" per the Office's

instruction with respect to claim 8. An appropriate correction has also been made to the spelling of "assay" in claims 30 and 31. Withdrawal of the objections to claims 8, 30 and 31 is therefore respectfully requested.

III. Rejection Under 35 U.S.C. 112, First Paragraph – Enablement

Claim 8, and claims 27-29 and 30-35, all of which dependent from claim 8, were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Claim 8, as amended, is directed to a method of screening or testing for candidate anti-fungal compounds by contacting a *Candida albicans* ATP(CTP):tRNA nucleotidyltransferase enzyme (CCA1) under the control of a heterologous promoter with one or more candidate compounds and determining whether the candidate compound inhibits growth or viability of the cell(s), and determining whether the candidate compound is a CCA1 inhibitor in a growth inhibition assay, a binding assay, a translation-inhibition assay, or a tRNA nucleotidyl transferase assay.

The Office maintained the enablement rejection for the same reasons made of record in the previous office action mailed on December 27, 2007. Specifically, the Office asserted that:

> Although, one can use [the assay of Example 3] to determine the direct effects of a compound on CCA1 protein, the claim, however is drawn to cell based screening or testing for candidate anti-fungal. The claims do not recite that the CCA1 protein is purified and does not recite that the effect of a compound on purified CCA1 activity is determined. Thus, Applicant's arguments are not commensurate with the scope of the claims. The claims as written are clearly drawn to a cell bases screening or testing for candidate anti-fungal compounds and not to a screening or testing for candidate anti-fungal compounds that directly impair CCA1 protein activity.

Office Action, page 3-4.

The Applicant submits that the Office's rejection is moot in light of the amendments made to claim 8. The Applicant respectfully requests that these rejections be withdrawn.

IV. Rejection Under 35 U.S.C. 112, First Paragraph – Written Description

Claims 8, 27-29 and 30-35, were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Specifically, the Office asserts that:

> The...method of cell based screening or testing for candidate antifungal compound with the particular method steps a-e is not disclosed in the specification. Page 5 lines 22-35 does not disclose the above method with step 'e'. Example 1 and 2 in the specification is drawn to expression and purification of CCA1. Example 3 discloses an in vitro assay for determining CCA1 activity and does not disclose the method of claim 8 with steps a-e. Thus, the amendment to claim 8, particularly step e is deemed new matter.

Office Action, page 5. The Applicant respectfully traverses this rejection.

"The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than presence or absence of literal support in the specification for the claim language." *In re Kaslow*, 707 F.2d 1366 (Fed. Cir. 1983). When an applicant amends and points out where and/or how the originally filed disclosure supports the amendments, the burden shifts to the examiner of presenting evidence or reasoning to explain why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims. Manual Patent Examining Procedure (the "M.P.E.P.") § 2163.04, Eighth Edition, Fifth Revision (August 2006).

The Applicant draws the Office's attention to at least some of the locations in the Specification that reasonably convey to the skilled artisan that the Applicants had possession of the subject matter set forth in claim 8, and in particular the step of determining whether the candidate compound is a CCA1 inhibitor in a growth inhibition assay, a binding assay, a translation-inhibition assay, or a tRNA nucleotidyl transferase assay. First, the Specification provides that a "CCA1 inhibitor" is "any compound that impairs CCA1 function in the fungus. A compound that impairs CCA1 function may be one that, modulates, e.g. inhibits, the expression or activity of CCA1, interacts with

CCA1 or binds to CCA1. Furthermore, a compound that modulates the expression of CCA1 may interfere with the transcription of the gene encoding CCA1 or with the translation of mRNA encoding CCA1 in target organisms." Page 3, line 11-17. Moreover, the Specification provides that the assay for determining whether a candidate compound is a CCA1 inhibitor may comprise a growth inhibition assay, a binding assay or a translation-inhibition assay, or nucleotidyltransferase assay. Page 4, line 12; example 3 and page 10, lines 15-37.

For at least the foregoing reasons, the Applicant asserts that claim 8 is supported with adequate written description for the recited subject matter and is in condition for allowance. Withdrawal of this rejection is therefore respectfully requested.

V. Rejection Under 35 U.S.C. 103(a)

A. Claim 1

The Office maintained the 103(a) rejection to Claim 1 as set forth in the previous office action. Applicant respectfully traverses this rejection. Claim 1 is directed to a method for screening or testing for candidate anti-fungal compounds that impair *Candida albicans* ATP(CTP):tRNA nucleotidyltransferase enzyme (CCA1) activity comprising contacting fungal *Candida albicans* CCA1 with one or more candidate compounds and determining the ability of the candidate compound to inhibit CCA1 activity.

The Office based the instant rejection of claim 1 over several references, including Weinstock et al. and Onishi et al. (both cited in previous action). Specifically, the Office asserts that:

> One of skill in the art would recognize CCA1 as an essential gene in general. CCA1 (ATP(CTP):tRNA nucleotidyltransferase) also known amongst many synonyms as tRNA nucleotidyltransferase or CCA-adding enzyme is a ubiquitous enzyme that catalyzes the incorporation of CMP and AMP into incomplete tRNA chains. The enzyme is required for normal growth of cells and is involved in repair of tRNA molecules that are missing part of the 3' terminus (see introduction of Navarro et al. 1991, Italian Journal of Biochemistry; 40(5) pages 295-303 and review article, Weiner, 2004, Current Biology, vol. 14, issue 20 pages R883-R885, both cited previously). Further, Hanic-Joyce et al. (Yeast 2002, 19:1399-1411) teach that mutations of essential residues in CCA1 is lethal to *Candida glabrata* (p.1406 column 2). Thus, since the enzyme is required for normal growth of cells and has been shown to be essential to C. glabrata, said CCA1 of *C. albicans* is expected to also be essential for the normal growth of the fungi.

Office Action, page 8. Therefore, the Office finds support for the instant rejection under § 103(a) in Weinstock et al. in view of Onishi et al., Navarro et al., Weiner and Hanic-Joyce et al. Applicants respectfully traverse this rejection.

The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d 1385, 1396 (2007) noted that the analysis supporting a rejection under 35 U.S.C. § 103 should be made explicit. *Id.* The examiner bears the initial burden of factually supporting any prima facie conclusion of obviousness. M.P.E.P. § 2142. The examiner's burden includes the requirement to assert that all the claimed elements were known in the prior art. M.P.E.P. § 2143.02. The prior art can only be modified or combined to reject claims as prima facie obvious when there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

1. Weinstock et al

The Office maintains that Weinstock et al. teach a method of screening test compounds for anti-fungal activity comprising providing a *Candida albicans* target polypeptide sequence such as *Candida albicans* CCA1 (citing table 2, columns 587 and 588 contig3807) and contacting a test compound with said CCA1 and further selecting antifungal candidates. Office Action, p. 6. This is inconsistent however with the admission that Weinstock et al. does not disclose determining the ability of the candidate compound to inhibit CCA1 activity. Office Action, p. 7. Applicant further points out that Weinstock et al. also does not disclose the CCA1 gene from *Candida albicans*, much less disclose any assays of CCA1 activity or that the CCA1 from *Candida albicans* is a target for antifungal candidates.

Rather, Weinstock et al. disclose CCA1 from *Saccharomyces cerevisiae*. See table 2, columns 587 and 588 contig3807. However, even for relatively closely related organisms such as *Saccharomyces cerevisiae* and *Candida albicans*, there are significant differences between the species that make such *in silico* predictions of the type made in Weinstock et al. unreliable. See, e.g., Specification, page 2, lines 1-3.

As the applicant further points out in the Specification, it is known that not all proteins essential in *Saccharomyces cerevisiae* are also essential in *Candida albicans*. For example, CET1 and CDC25 are not essential in *Candida albicans* despite being essential in *S. cerevisiae*. Specification, page 2, lines 3-5. Furthermore, genome wide

identification of essential genes has not been successfully applied to *Candida albicans* for several reasons. These reasons include that *Candida albicans* is a diploid organism, is not capable of mating under normal circumstances, and that there are few functional transposable elements. Specification, p. 2, lines 17-19. Thus, without prior knowledge that *Candida albicans* CCA1 is an essential gene, a skilled artisan would not have a reasonable expectation of success in screening for candidate antifungal compounds.

2. Onishi et al.

According to the Office, Onishi et al. allegedly teach a method for screening or testing candidate anti-fungal compounds in vitro by determining whether the candidate anti-fungal inhibit the activity of a target *Candida albicans* protein and a method for screening candidate antifungal compounds by determining the effect of the compounds on growth and viability of *Candida albicans* cells. Office Action, p. 7. However, Onishi et al. does not disclose the CCA1 gene from *Candida albicans*, much less the disclosure of any assays of CCA1 activity or that the CCA1 from *Candida albicans* is a target for antifungal candidates.

3. Hanic-Joyce et al.

Without admitting or conceding in any manner to the 103(a) rejection based on Hanic-Joyce et al. and solely to expedite the prosecution of the present application, Applicants submit herewith a declaration under 37 C.F.R. § 131 antedating the Hanic-Joyce publication date of October 31, 2002. M.P.E.P. § 715(I)(B). Because only the named inventor of the instant application contributed to the subject matter as defined in the claims of the instant application at a date prior to October 31, 2002, Applicants submit that the Hanic-Joyce date of publication was not "before" the inventive date of the instant application, as required in order for a reference to qualify as prior art under § 102(a)/103(a).

4. Weiner

Similarly, the Weiner reference does not serve as prior art in this case. The instant application is a national stage entry of PCT/GB03/05373, with an international filing date of December 9, 2003, claiming a right of priority under the Paris Convention to United Kingdom patent application no. 0228702.7, filed December 9, 2002. See 37 C.F.R. § 1.55; M.P.E.P. § 201.13. Because the Weiner reference was published in 2004,

it therefore does not qualify as prior art with respect to the instant application under § 102(a)/103(a).

5. Navarro et al.

The Office alleged that the Navarro et al. disclose that the CCA1 enzyme is required for normal growth of cells and is involved in repair of tRNA molecules that are missing part of the 3' terminus. Applicant points out that Navarro et al. disclose that CCA1 –isolated from *Saccharomyces cerevisiae* –was inactivated in nitrogen starved yeast cells and yeast mutant cells lacking several proteases. Navarro et al., 1991, Italian Journal of Biochemistry; 40(5) pages 295-303. Significantly, Navarro et al. does not provide any support for *Candida albicans* CCA1, nor the disclosure that CCA1 is an essential protein to any species, much less the connection that CCA1 is essential in *Candida albicans*. Finally, Navarro et al. does not provide any support for the assertion that an assay could be utilized with target antifungal candidates of *Candida albicans* CCA1.

Because neither Hanic-Joyce et al. nor Weiner qualify as prior art with respect to the instant application, and because for the reasons set forth directly above, Navarro et al. does not provide any support that CCA1 is an essential protein to any species, the Office's assertion that "one of skill in the art would recognize that CCA1 to be an essential gene in general" (Office Action, p. 8) is not supported with an explicit reference as required of the Supreme Court in *KSR. KSR International*, 127 S. Ct. 1727. For this same reason, the Office has not established that all the claimed elements were known in the prior art before the effective filing date of the instant application. The conclusion that the prior art could be successfully modified or combined in a manner to render the subject matter of claim 8 obvious flies in the face of the knowledge of a person of ordinary skill as of the date of invention, as exemplified by the references discussed herein. *Merck & Co.*, 800 F.2d 1091.

For at least these reasons, the Applicant respectfully requests that the Office withdraw the rejection under 35 U.S.C. § 103(a).

B. Claims 23-26 and 30-32

Claims 23-26 and 30-32 were rejected under 35 U.S.C. 103(a) as being unpatentable over Weinstock et al. and Onishi et al. (both cited in previous action) as

applied to claim 1 further in view of Chen et al. (The Journal of Biological Chemistry, 1990, vol. 265, pages 16221-16224, cited in IDS).

Claim 23 is directed to the assay of claim 1, further requiring the determination of the ability of the candidate compound to inhibit CCA1 activity in a translation assay and/or a tRNA nucleotidyl transferase assay (step (d)). Claim 24 provides the further limitation that the determination of step d) is based only on a tRNA nucleotidyl transferase assay. Claim 25 further requires that the tRNA nucleotidyl transferase assay utilize a labeled nucleotide, and claim 26 requires a radiolabeled nucleotide.

Claim 30 is also directed to the assay of claim 8, but it specifically requires that the ability of the candidate compound to inhibit CCA1 activity as determined according to step e) be based on a tRNA nucleotidyl transferase assay. Claim 31 further requires that the tRNA nucleotidyl transferase assay utilizes a labeled nucleotide, and claim 32 requires a radiolabeled nucleotide.

With respect to claims 23-26 and 30-32, the Office Action sets forth that:

> Chen et al. teach an assay for measuring tRNA nucleotidyltransferase activity (aka CCA1) i.e. tRNA nucleotidyl transferase assay which uses labeled/radiolabelednucleotide (3H-CTP). It would have been prima facie obvious to one of ordinary skill in the art to use the enzymatic assay disclosed by Chen et al. for determining the activity of CCA1 (tRNA nucleotidyltrasnferase) in the method of Weinstock et al. and Onishi et al. as combined. The enzymatic assay for determining the activity of CCA1 is known in the art and it would have been within the skill of the ordinary artisan to adopt or adapt said enzymatic assay for determining the activity of CCA1 in the presence of candidate anti-fungal compound.

Office action, page 10. Thus, the Office basis its rejections on Weinstock et al. in view of Onishi et al. and Chen et al. The Applicant respectfully traverses these rejections.

As discussed in more detail above, neither Onishi et al. nor Weinstock et al. disclose *Candida albicans* CCA1 protein, let alone the fact that *Candida albicans* is an antifungal target or an assay for determining *Candida albicans* activity (of which claims 23-26 and 30-32 are dependent upon). The Office asserts that Chen et al. teach an assay for measuring CCA1 activity using labeled/radiolabeled nucleotide. Office Action, p. 10. However, Chen et al. describe the purification of CCA1 from *Saccharomyces cerevisiae*. Specification, page 2, lines 31-32. As discussed in more detail above, however, even for relatively closely related organisms such as *Saccharomyces cerevisiae* and *Candida*

albicans, there are significant differences between the two species that make predictions spanning across the two genera unreliable. Applicants submit that Chen et al. does not disclose an assay for CCA1 of *Candida albicans* as required of independent claims 1 or 8 (of which claims 23-26 and 30-32 are dependent upon).

Because Chen et al. does not disclose *Candida albicans* CCA1, Chen et al. adds nothing to the Applicants response with respect to claim 1. Therefore, for the same reasons as discussed with respect to claim 1 above, the Office has not established that all the elements of claims 23-26 and 30-32 were known in the prior art before the effective filing date of the instant application. Applicant respectfully submits that the Office has not met its burden to establish a prima facie case of obviousness, and thus the rejections should be withdrawn.

C. Claims 8, 27-29 and 33-35

Claims 8, 27-29 and 33-35 were rejected under 35 U.S.C. 103(a) as being unpatentable over Georgopapadakou et al. (Expert Opin. Investig. Drugs (2002) 11 (8):1117-1125) in view of Weinstock et al., Nakayama et al. (Infection and Immunity, Dec. 2000, p. 6712-6719) and Onishi et al. Specifically, the Office asserts that:

> It would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to screen for candidate compounds that impair the activity of C. albicans CCA 1 disclosed by Weinstock et al using the methods disclosed by Georgopapadakou et al and Nakayama et al and Onishi et al because Georgopapadakou et al teach that a cell based screening methods using tetracycline inducible/regulatable gene expression in C. albicans can be used to screen for inhibitors of C. albicans enzyme and Nakayama et al teach said method of tetracycline regulatable system of gene expression in C. albicans which uses a tetracycline inducible heterologous tet promoter. It is obvious that said cell based screening method will involve the determination of the effect of said compound on the growth and viability of said C. albicans (since the method is directed at cell based screening for an antifungal compound) and it would be prima facie obvious to compare the growth or viability of said C. albicans when the tet promoter is repressed (no CCA1 expression) as a control to determine any differences in the effect of compounds on the growth or viability of C. albicans in the presence of CCA1 expression. Further it is obvious that validation tests are further carried out to determine that said candidate antifungal compound inhibits CCA1 activity directly as taught by Onishi et al who teaches a cell based screen for antifungal activity of several compounds (which putatively inhibit an enzyme's activity) by a growth inhibition assay (page 369 column 1 materials and methods and table 1) and then the compounds were evaluated to determine whether said compounds were direct inhibitors of the enzyme by measuring the enzyme's activity in the presence of said compounds (page 370 column 2 first full paragraph, page 373 column 1 – 2 and table 4).

Office Action, page 12. Therefore, the Office finds support for the instant rejection under § 103(a) in Weinstock et al. in view of Georgopapadakou et al., Nakayama et al. and Onishi et al. Applicants respectfully traverse this rejection.

As set forth above, neither Weinstock et al. nor Onishi et al. teach the method of screening test compounds for antifungal activity by contacting a candidate compound with providing *Candida albicans* CCA1 as required by independent claim 8. Similarly, neither Georgopapadakou et al. nor Nakayama et al. disclose *Candida albicans* CCA1 as the targeted protein of the assay of claim 8.

1. Georgopapadakou et al.

The Office Action asserted that Georgopapadakou et al. teach a cell based screening for candidate inhibitors of a specific enzyme of *Candida albicans* using a *Candida albicans* tetracycline regulatable promoter system which comprises providing said *C. albicans* expressing the enzyme under tetracycline. Office Action, p. 12. The specific enzyme targeted is the N-myristoyltransferase enzyme of *Candida albicans*. Georgopapadakou et al., page 1119, column 2. Georgopapadakou et al. further teach that the N-myristoyltransferase enzymes inhibit the transfer of the 14-carbon saturated fatty acid myristate from CoA to the amino-terminal glycine which is exposed after removal of the initiator methionine of eukaryotic and viral proteins. Page 1119, column 2. Thus, Georgopapadakou et al. do not teach the tRNA nucleotidyltransferase (CCA1) enzyme as recited in claim 8, but rather teach a different enzyme, responsible for an entirely different function than that of CCA1.

2. Nakayama et al.

The Office Action alleged that Nakayama et al. teach a tetracycline system of gene expression in *Candida albicans* which uses a tetracycline inducible heterologous tet promoter inducible in the absence of doxycline or tetracycline and repressible in the presence of doxcycline or tetracycline. Office Action, p. 12. However, Nakayama et al. do not teach an inducible regulation system of the CCA1 gene encoding the CCA1 protein. Significantly, Nakayama et al. recognize the difficulty in identifying genes of *Candida albicans* because of its diploid genome which compounds the difficulty in isolating haploid strains. Page 6712. As such, Nakayama et al. teach only the regulation of the tetR-ScHAP4AD gene. Page 6712.

The Office has not established that all elements of independent claim 8 and dependent claims 27-29 and 33-35 existed in the prior art before the effective filing date of the instant application because prior to the instant invention it was not known that the essential *Candida albicans* CCA1 protein was a viable antifungal target. Neither Georgopapadakou et al. nor Nakayama et al. alter this conclusion. Further, the Office has not come forth with an explicit teaching, suggestion, motivation, or any other basis to which a skilled artisan could base a reasonable expectation of success that *Candida albicans* CCA1 could serve as an antifungal target in the assay as defined by the claims.

Applicant respectfully submits that the Office has not met its burden to establish a prima facie case of obviousness, and thus the outstanding rejections to the pending claims should be withdrawn.

CONCLUSION

For at least the foregoing reasons, it is respectfully submitted that claims 1, 8, and new claims 23-35, are in condition for allowance. Early and favorable consideration is respectfully requested, and the Examiner is encouraged to contact the undersigned at (858) 350-2300 with any questions or to otherwise expedite prosecution.

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